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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/814,633	04/01/2004	Van Hung Truong	2201.0020000/RWE	7438

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EXAMINER	
SIMMONS, CHRIS E	
ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/814,633	TRUONG, VAN HUNG	
	Examiner	Art Unit	
	Chris E. Simmons	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-12 and 19-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-12 and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/23/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims:

The amended claim set submitted on 10/19/2007 is acknowledged. Cancellation of claims 4, 13-18 and 22-26 is acknowledged.

Claims 1-3 and 5-12- and 19-21 are presented for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-12 and 19-21 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Instant independent claim 1 recites the limitation "wherein said buffer solution is an acetate buffer solution containing less than 0.2% acetate or a citrate buffer solution containing less than 0.1% citrate". The specification lacks any description that supports the limitation of an "acetate buffer solution containing less than 0.2% acetate or a citrate buffer solution containing less than 0.1% citrate". The range of less than 0.2% acetate and less than 0.1% citrate introduces new matter that includes levels not conveyed in the specification.

On page 13, under EXAMPLE 2:Buffer/pH Optimization, lines 24-27, Applicant recites, "It was, however, common in injectable products to include sodium acetate trihydrate at levels between 0.00006-0.2%. The 0.07% level used in the formulations of Example 1 is well within this range. It was also known that citrate buffers found in inhalation products were present at levels that did not exceed 0.1%".

This is support only for sodium acetate trihydrate at levels below 0.2% - not acetate levels less than 0.2%. This recitation also supports citrate buffers at levels less than 0.1% - not citrate buffer solutions containing less than 0.1% citrate.

Response to Amendments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 5-12 and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Asmus et al. Stability of Frozen Methacholine Solutions in Unit-Dose Syringes for Bronchoprovocation. Chest 121:1634-1637 (May 2002) and Watson et al. Effect of pH on the stability of methacholine chloride in solution. Respiratory Medicine (1998) 92,588-592 and (Website) Practical Engineering Data & Tools for Medical Device Professionals: Selecting a Sterilization method (2001) http://web.archive.org/web/20030112130541/http://engineeringreference.com/Sterilization/select+sterilization.htm in view of (FDA) http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm in further view of ScienceLab.com A, Material Safety Data Sheet: Sodium Acetate Anhydrous MSDS and ScienceLab.com B, Material Safety Data Sheet: Sodium Acetate Trihydrate MSDS.

Asmus et al. teach a formulation of methacholine chloride wherein the concentration of methacholine is less than 0.25 mg/mL (see Abstract), sodium chloride is used as a diluent (see Abstract), the pH is from 4 to 5 (see Abstract) wherein the reference is directed to stabilizing the solution and teaches that the pH should be slightly acid since pH levels above 6 encourage hydrolysis of the solution and loss of potency (see page 1634) as well as directed to a process of making a sterile solution (see Materials and Methods on page 1635) which are further stored in plastic syringes (see Results page 1636).

Asmus et al. do not teach a methacholine solution comprising acetate and a

preservative whereby the solution is sterilized by aseptic filtration.

Watson et al. teach a methacholine chloride solution comprising sodium chloride (see Introduction page 588) and acetate at a concentration of 0.02M (see page 598) wherein the reference further teaches that methacholine rapidly decomposes due to hydrolysis under basic conditions (see Discussion page 591) and that being the basis of studying varying buffers and pHs which leads one of ordinary skill in the art to vary and optimize the concentration of acetate depending on the solution variables and desired resultant pH. Watson et al. also teach that phenol (considered a preservative since it is inhibiting contamination) can be added to the solutions to inhibit microbial growth (see Discussion page 592) thereby encouraging sterile solutions.

The Practical Engineering reference teaches a process for sterilizing liquid products comprising aseptic processing and filtration (see item 5). The reference further explains that many liquid pharmaceutical products cannot withstand thermal sterilization and that such are relegated to aseptic filtration and then filled into presterilized containers such as vials, ampoules or syringes (see item 5).

FDA teaches that the sodium citrate maximum level in a solution for inhalation is 0.6%. In addition, ScienceLab.com A and B teach that sodium acetate anhydrous and sodium acetate trihydrate are both respiratory irritants.

One of ordinary skill in the art would have been motivated to combine the above references because Asmus et al. and Watson et al. are both directed to stable solutions of methacholine. Moreover, both teach that pHs over 6.0 lead to destabilization and hydrolysis of the active agent therefore suggesting a lower pH which Watson et al. teach by adding acetate to the solution. One of ordinary skill in the art would be motivated to make an inhalable solution comprising methacholine in a buffer solution comprising acetate or citrate levels that are within FDA approved levels. The skilled artisan would especially want to make the solution comprising a bronchoconstrictor such as methacholine with low levels of acetate since, as taught by ScienceLab.com, sodium acetate trihydrate and sodium acetate anhydrous are respiratory irritants. The skilled artisan will be further motivated if the composition is administered to asthmatic patients. Both Asmus et al. and Watson et al. teach sterile solutions since the solution will be inhaled by a patient, which directs one of ordinary skill in the art to a method of sterilization. The Practical Engineering reference specifically teaches that liquid pharmaceuticals can be sterilized by aseptic filtration since they cannot withstand thermal sterilization. Therefore, one of ordinary skill in the art would expect a successful sterilization process by employing the Practical Engineering reference. Thus, the combined references teach and make prima facie obvious how to use the claimed, invention at the time that it was made.

Response to Arguments

Applicant asserts that the methacholine chloride solutions disclosed in Watson cannot be considered to be "inhalable." As set out in the present application, the levels of the acetate and citrate buffers must be sufficiently low to not independently cause bronchoconstriction or bronchoirritation. Amended claim 1 recites that the buffer solution is an acetate buffer solution containing less than 0.2% acetate or a citrate buffer solution containing less than 0.1% citrate. These levels do not independently cause bronchoconstriction or bronchoirritation and are within acceptable levels of pharmaceutically acceptable buffering agents as provided by government regulatory agencies. For example, the United States' Food and Drug Administration has an Inactive Ingredient Guide (IIG) (accessible to the public at http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm) that provides a listing of excipients with maximum acceptable concentration amounts.

Applicant further asserts that there is nothing in Asmus, taken alone or in combination with Watson that suggests that the use of acetate or citrate buffers having concentrations of acetate or citrate suitable for inhalation would inevitably result in stable formulations of methacholine chloride. Buffering capacity is the ability of a buffer to resist changes in pH. There are two components that affect buffering capacity: the first is the pKa (buffering capacity is maximized at a pH close to the pKa of a buffeting agent); and the second is molarity (buffering capacity is increased by increasing the concentration of the buffering agent). There is nothing in Watson that teaches or

suggests that solutions containing lower concentrations of a buffering agent, and that thus have lower buffering capacities, than those specifically disclosed in Watson would successfully prevent or minimize methacholine hydrolysis. In fact, Watson suggests that higher concentrations of buffering agents are preferred and, thus, teaches away from the lower concentrations set forth in the claims. At best, it might be considered "obvious to try" to see if lower concentrations of buffers might give a stable product. However, "**obvious to try**" is not a proper standard for determining obviousness under 35 U.S.C. § 103(a).

Applicant's assertions are not persuasive. The Office holds the position that one of ordinary skill in the art would be motivated to decrease the amounts of the acetate or citrate levels in the old composition to make a composition comprising levels within acceptable levels of pharmaceutically acceptable buffering agents as provided by government regulatory agencies. Since it is well known that sodium acetate trihydrate and sodium acetate anhydrous are respiratory irritants, the skilled artisan would by motivated to decrease these amounts in a composition for inhalation. Furthermore, it would be obvious to try to make the invention as claimed since a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. The skilled artisan would have recognized the desirability to make a solution of the bronchoconstrictor, methacholine, in a stable solution at a pH level between 4 to 6 as taught by Watson and Asmus using levels of the acetate or

citrate buffer taught by Watson that are low enough to not contribute to respiratory irritation such as bronchoconstriction and are within the FDA guidelines.

With regards to Applicants assertion that of In re Wiggins supports Applicant's arguments, the Office asserts that in *Wiggins the* claims required the presence of a "pharmaceutical diluent" as part of the compositions, whereas Wolf does not explicitly mention the use of such a diluent or carrier in administering "O 2" to mice. However, in the instant application, the presence of citrate or acetate is required as is explicitly taught in *Watson*. Applicant's argument is not persuasive.

Conclusion

Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chris E. Simmons whose telephone number is (571) 272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Chris Simmons
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AU 1614

August 22, 2007

8/27/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

JDA